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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,446	10/24/2000	Suzana Petanceska	0630/1G184-US1	2608

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,446	PETANCESKA ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,20,22-25 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 20, 22-25 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The RCE filed on 12-9-05 is acknowledged.

Claims included in the prosecution are 1-6, 20, 22-25 and 31.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2, 4-6, 20, 22-25 and 31 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the level of amyloid-beta peptides in vivo by administering 17 beta estradiol, does not reasonably provide enablement for a method of delaying or reducing the likelihood or ameliorating a disease or disorder associated with amyloidosis and which diseases include Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Instant invention is based on the apparent decrease in the levels of amyloid beta peptides using estradiol at a dose, which does not affect the soluble APP levels. First of all, as evident from the literature (Jaffe et al (JBC of record), treatment with physiological levels of estradiol in vitro results in large increases in soluble APP and according to applicant that observing no effect on this soluble APP levels is surprising after estradiol administration. However, instant claims are drawn to 'estrogen compound' and according to instant specification

on pages 8 and 9 multitudes of compounds having a steroidal structure fall within this generic term. There is no evidence in instant specification that in vivo administration of any compound falling within this generic term would lead to the same surprising results. There is no adequate guidance in the specification as to how one can determine the amounts of the compounds, which would not have an effect on the soluble APP, but decrease the levels of beta peptides. Furthermore, there is no evidence presented in the specification as to how one can predict the susceptibility of a human to Alzheimer's disease and how the treatment of these people with estrogens would delay or reduce the likelihood or ameliorating Alzheimer's disease, let alone other diseases wherein amyloidosis is involved. Broad claims must have broad basis of support in the specification; in the absence of such support, claims must be limited to estradiol effect on amyloid beta peptide levels without having an effect on the soluble APP; it would require undue experimentation to determine which of the compounds falling within the definition of 'estrogen compound' would have the same effect. In this context, it should be pointed out that the reference of Heikkinem et al (Experimental Neurology, 2004) submitted by applicant teaches that Estrogen treatment does not affect beta amyloid accumulation and plaque formation thus, showing the unpredictability in the treatment of Alzheimer's disease.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that instant specification describes in detail various estrogen compounds and methods for testing Estrogen compounds and for determining effective amounts of estrogen compounds. Applicant further argues that the

specification contains working examples describing in vivo administration of 17 beta-estradiol to overiectomized animals and the resulting reduction in A beta levels without decrease in soluble APP. These arguments are not found to be persuasive. The results presented in the specification using overiectomized guinea pigs are rather confusing. First of all, as evident from the table on page 24 of the specification (also Figure 2 A), the intact animals themselves have low levels of A beta (1.568 :col. 1, intact : brain tissue). This value is the lowest compared to the E2 administered values both at low dosage and high dosage (2.063 and 2.094 respectively). The very fact that that the intact animals have the lowest levels indicate that the physiological levels of estrogen is sufficient to maintain the low levels of A beta and even high administered dosage of E2 is unable to restore the levels of A beta present in intact animals. Both low and high dosages of E2 produce the same effect on A beta levels in overiectomized animals. Based these findings it is unclear as to how one can screen the estrogen compounds for their effect on A beta levels and even extrapolate the results and recite claims in terms of 'delaying or reducing the likelihood of, or ameliorating, a disease or disorder associated with Ab amyloidosis which includes even Alzheimer's. As pointed out before, according to the specification, even testosterone and other steroids, which lead to the formation of various estrogens and testosterone, are included in the generic term. Mammalian bodies produce estrogens and testosterones and the amounts of the administered estradiol appear to be close to the physiological levels (on Kg basis) in humans. As already pointed out above, there is evidence in the literature regarding the unpredictability regarding estrogen treatment, beta amyloid accumulation, plaque

formation and Alzheimer's disease. Applicant's arguments based on the reference of Zandi are not persuasive. This reference concludes that "prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use ***unless such use has exceeded 10 years***". Instant claim 20 does not recite any time period and claim 22 appears to indicate the time period for the ameliorating or delaying or reducing the disease as at least 10 days. Instant specification provides no data to show that one can achieve these with Alzheimer's. It is also interesting to note from instant figure 3 that the differences observed for soluble APP levels in intact, ovX, 1 mg/Kg and 5 mg/Kg groups are insignificant. This implies that estrogen at any dosage including physiological levels of estrogens have no effect on s APP levels. The rejection is maintained.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 (which is dependent from claim 1) is directed to administering a Conjugated estrogen compound in an amount such that it reduces A beta levels without affecting the soluble APP levels and the parent claim 1 is drawn to **animals.** Since the term animals included a variety of animals, which are different genetically from humans, and also since the term includes human males and females, it is natural to assume that the amount of the conjugated estrogen to be administered also varies meeting the

limitations in claim 1. Claim 31 however, recites specific amounts of the conjugated estrogen. There is no evidence that the amounts recited will not affect the APP in all animals and in human males and females. Claim 31 appears to be inconsistent with claim 1 limitation of 'animals'.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 20, 22, 23, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Simpkins (5,554,601).

Simpkins teaches the neuroprotective effect and treatment of the neurodegenerative disorder, Alzheimer's disease by administering 17-b-estradiol. The composition is either administered daily or by a control release device (abstract, col. 10, lines 4-19 and 26-33, Example 3b on col. 17 and claims). Simpkins does not discuss the APP levels; it should be pointed out however, that mechanism by which estradiol exerts its activity has no patentable significance.

7. Claims 20, 23, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Washburn (5,719,137).

Washburn discloses the effectiveness of 7 alpha dihydroequilenin and compares it with estradiol in a method of reducing the risk of Alzheimer's disease and the

method of treating other dementia related conditions in males and females. The composition is administered in a transdermal patch (control release) (abstract, col. 3, lines 22-60, col. 8, lines 2-3, examples and claims). The reference meets the requirements of instant claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that The 137 patent discloses the use of 17 a-dihydroequilenin and not 17 b-estradiol for the prevention of neurodegeneration and cognitive dysfunction associated with AD and other dementia related disorders. Applicant is incorrect in making this statement since Example 2 on columns 5 and 6 of Washburn clearly shows comparisons between 17 beta-estradiol and 17 a-dihydroequilenin. The reference still meets the requirements of instant claims.

8. Claims 1-3, 5-6, 20, 23-25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/43647 of record.

WO teaches administration of 17 beta-estradiol at dosages of 0.01 to 25 mg/Kg body weight, in particular, a single dosage of 1, 5 and 10 mg for the reduction of APP fragments which include A beta (abstract, page 14, lines 6-13. WO further teaches methods for alleviating an impaired condition brought on by neurodegenerative or cognitive changes (claim 22). The formulations include controlled release formulations (page 15, lines 16-23). Since the dosages taught by WO are the same as in instant invention, the effect of the estrogen compound on sAPP levels and the ratios of A beta peptides would be the same.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Washburn (5,719,137) or WO 98/43647 cited above.

The teachings of Washburn and WO have been discussed above. What is lacking in Washburn and WO is the administration to be for at least 10 days. Since this parameter depends upon various factors such as the severity of the condition and the age of the patient, it is deemed to be an obvious parameter manipulatable by an artisan to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that 137 patent does not teach or suggest any dose of 7 alpha-dihydroequilenin that has nay effect on A beta or on the soluble APP levels. This argument is not found to be persuasive since as pointed out above, the mechanism by which a compound acts in treating a disease has no significance. Furthermore, applicant himself has not shown that Alzheimer's disease can be ameliorated with compounds, which a mammalian body normally produces, or numerous compounds falling within that definition.

11. Claims 22, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al cited before.

The teachings of Xu have been discussed before. What are lacking in Xu et al is the use of estrogens other than estradiol, the use of estrogens in a controlled release device, the amounts and the protocol of administration. It would have been obvious to one of ordinary skill in the art to use instant conjugated estrogen with a reasonable expectation of success since estrogen receptors are the same and the conjugated estrogen is used in the art in estrogen replacement therapy. The use of a controlled release device such as a transdermal patch would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success, since these are available commercially. Instant protocol of administration (for 10 days) and the amounts are deemed to be a manipulatable parameter since as pointed out above, this depends on various factors such as the severity of the condition and the age of the patient.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Xu teaches away from instant invention because in Xu, the soluble APP levels are increased. This argument is not found to be persuasive since the rejected claims are drawn to "a method of delaying or reducing the likelihood of or ameliorating, a disease or disorder" and the disorder claimed is Alzheimer's disease. Xu is clearly suggestive of delaying or preventing AD and the mechanism by which the same claimed compound taught by the prior art works has no significance.

12. Claims 1-6, 20, 22-25 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48488 in combination with Washburn (5,510,342), Holland

(3,843,662) or Lundeen (Endocrinology, vol. 138, pp. 1552, 1997) individually or taken together.

WO teaches that blood cholesterol levels correlate with the production of amyloid protein and are predictors of populations at risk of developing Alzheimer's disease (AD). According to WO, methods of lowering cholesterol can be used to decrease production of A beta, thereby decreasing the risk of developing AD (abstract, pages 1-6, Example 3 and claims). What is lacking in WO is the use of estrogens.

Washburn discloses that estrogens and conjugated estrogens lower blood cholesterol (table 1 on col. 4; col. 7, line 67 through col. 8, line 22).

Holland teaches that lowering of blood cholesterol by estrogens is known (col. 1, lines 25-28).

Lundeen similarly teaches that estrogens (estradiol and ethinyl estradiol) reduce plasma cholesterol levels (abstract, Results and Discussion).

It would have been obvious to one of ordinary skill in the art to use estrogens in the teaching of WO, that is, for lowering the levels of A beta peptide and decrease the risk of developing Alzheimer's disease since Washburn, Holland, and Lundeen teach that estrogens and conjugated estrogens lower cholesterol and because WO teaches that methods of lowering cholesterol can be used to decrease production of A beta, thereby decreasing the risk of developing AD. In the absence of showing the criticality, instant doses and protocol of administration are deemed to be obvious parameters manipulated by an artisan since these depend upon the severity of the condition and the age of the patient.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that 488 does not teach estrogen compounds, their doses that reduce A beta levels and not affecting APP levels. These arguments are not found to be persuasive since WO clearly establishes the correlation between cholesterol levels, amyloid proteins and Alzheimer's disease and shows the effect of cholesterol lowering compounds in lowering the production of A beta thereby decreasing the risk of developing AD. Therefore, instant method would have been obvious to one of ordinary skill in the art based on the combined teachings of WO, Washburn, Holland or Lundeen. Furthermore, as pointed out above, a careful examination of Fig. 3 in the specification indicates no changes in soluble APP levels in intact animals, animals deprived of the physiological levels of estrogens and estrogen administered at 1 mg and 5 mg dosages. This shows that estrogen at any dosage level does not affect the s APP levels. Applicant's arguments based on Fagan et al's reference which apparently show no differences in the A beta pathology in PDAPP mice of various apoAI genotypes despite robust differences in plasma cholesterol levels between the groups are not persuasive. WO teachings are based on human neuronal cultures whereas Fagan et al's study is based on rat model. This shows that the results vary with different models and one would expect the same with applicant's studies; instant claims however, are drawn to 'animals' in general which includes human males and females and 'generic' estrogen compounds. Since WO's teachings are based on human neurons, it would be obvious to one of ordinary skill in the art that the results can be extrapolated to in vivo administration to humans with a reasonable expectation of success. As pointed out

before, instant specification neither shows no unexpected results in terms of treating the diseases claimed nor establishes the criticality of the soluble APP levels.

13. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/43647 in view of Simpkins (5,554,601) both cited above.

The teachings of WO and Simpkins have been discussed above. What is lacking in WO is the teaching of conjugated equine estrogen. The use of a conjugated estrogen instead of estradiol taught by WO would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Simpkins teaches the equivalency between these two compounds (col. 4, lines 50-61 and Table II).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK